# CASE REPORTS

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## Coccidioidal Meningitis

### The Use of Amphotericin B Intravenously and Intrathecally by Repeated Lumbar Punctures

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COCCIDIOIDAL MENINGITIS in children continues to be a major cause of granulomatous meningitis and was uniformly fatal before the advent of amphotericin B therapy. The use of amphotericin B has presented many problems related to dosage, duration of therapy and toxicity of the drug—chiefly on the kidney. Winn has reported that cisternal injection is the best method in treating adults with coccidioidal meningitis.[1]

This report describes the clinical and laboratory findings and response to therapy in a child with coccidioidal meningitis treated with amphotericin B administered intravenously and intrathecally by lumbar puncture. Cisternal injections were not given.

#### Report of a Case

A 2¾-year-old white boy was admitted to Children's Hospital of San Francisco in 1971 for the evaluation of fever, cough, vomiting and increasing lethargy. The patient was in reportedly good health until six weeks before admission, when the mother consulted a physician because the child had fever and was coughing and vomiting. An infection was suspected and treatment was begun using acetysalicylic acid and then penicillin and sulfisoxazole (Gantrisin®). However, intermittent fever with temperatures up to 101°F (38.3°C), and decreased activity continued and the patient was admitted to the local hospital.

On physical examination at admission, the patient was seen to be well nourished, alert and active. There were no abnormal findings except fever elevation. A workup for acute infection was carried out, including a lumbar puncture. There were no abnormalities discovered except for the cerebrospinal fluid (CSF) which contained 204 leukocytes, with 74 percent neutrophiles and 26 percent lymphocytes. Cerebrospinal fluid protein was 60 and glucose was 20 mg per 100 ml. Partially treated bacterial meningitis was suspected and treatment was begun with ampicillin and, subsequently, chloramphenicol. Blood and CSF cultures subsequently showed no growth. Response to a skin test for tuberculosis was negative, and a skin test for coccidioidomycosis showed 1 cm of erythema at 48 hours, but no induration. The child continued febrile and very irritable in spite of therapy and was then transferred to Children's Hospital of San Francisco.

Review of the medical history showed that the child resulted from the mother's first pregnancy, which was full term and normal. He was born at the local hospital in Visalia, California in the San Joaquin Valley. Birth weight was 8 pounds, 13 ounces, and no neonatal problems were encountered. The developmental milestones were passed normally with the child walking at eleven months and talking at 12 months. There was no history of serious illness, convulsive disease, high fevers, pneumonia or allergies to food or medication. The patient had never before been admitted to hospital and had lived only in California. The family history was unremarkable; the mother and father were living and well and a 9-month-old sister was in good health.

On physical examination at admission, the patient was found to be very irritable, with a tem-

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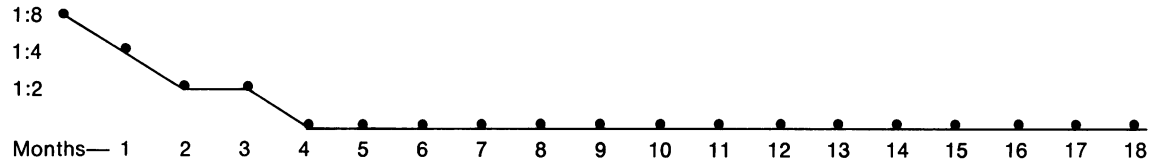


**Chart 1.**—Cerebrospinal fluid complement fixation titers for coccidioides immitis. (Studies done by Demosthenes Pappagianis, MD, PhD, University of California, Davis, School of Medicine)

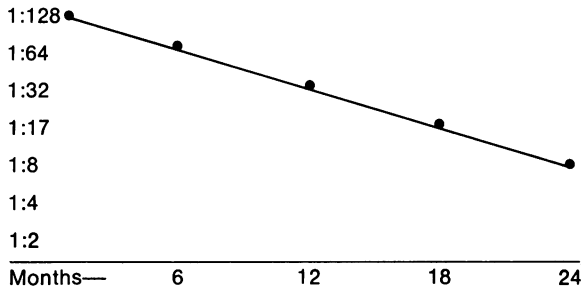


**Chart 2.**—Serum complement fixation titers for coccidioides immitis. (Studies done by Demosthenes Pappagianis, MD, PhD, University of California, Davis, School of Medicine)

perature of 103°F (39.4°C). Apparent frontal cranial enlargement along with minimal gait ataxia was noted but the remainder of the physical examination, which included a detailed neurological examination, was unremarkable.

Laboratory analysis showed a hemoglobin count of 10.9 grams per 100 ml, leukocytes 16,300 per cu mm, with 64 percent neutrophiles, 28 percent lymphocytes and 6 percent monocytes. Results of urinalysis were normal. Lumbar puncture done on admission showed an opening pressure of 380 mm of water with good dynamics and a closing pressure of 320 mm. The fluid was clear. Examination of the CSF showed 91 cells, 74 percent lymphocytes and 26 percent neutrophiles. The CSF protein was 33 and the CSF glucose was 12 mg per 100 ml (blood glucose 87 mg per 100 ml). Gram stain, India ink preparation and acid fast smear showed no organisms. The total lactic acid dehydrogenase in the CSF was 8 units (normal 5 to 25 units). Roentgenograms of the skull showed spreading of sutures. Bilateral carotid and vertebral cerebral arteriography were carried out and showed diffuse swelling of the brain, with a localized swelling posteriorly in the left temporal lobe. There was evidence of perivascular disease constricting the arteries and veins over the surface of the brain. No abnormalities were noted on brain scan.

Coccidioides immitis complement fixation titers were positive in both the serum and cerebral spinal fluid (Charts 1 and 2). Precipitins for coccidioidomycosis were negative and remained negative. Response to a skin test for coccidioidomycosis was negative at 48 hours.

Laboratory studies showed serum electrolytes of sodium 140 milliequivalents (mEq), potassium 4.0 mEq, chloride 105 mEq, carbonic acid 20 mEq, blood urea nitrogen 6 mg per 100 ml and creatinine 0.5 mg per 100 ml. The febrile agglutinins were negative. Immunoglobulins showed immunoglobulin A (IgA) 230 mg per 100 ml (normal range 39 to 113), immunoglobulin G (IgG) 1,000 mg per 100 ml (normal range 556 to 1,272), and immunoglobulin M (IgM) 140 mg per 100 ml (normal range 55 to 139). Serum lead level was normal. Roentgenograms of the chest and skeletal survey showed no abnormalities. A bone marrow study showed myeloid hyperplasia only. Cultures for bacteria, fungi and tuberculosis were negative. Results of viral agglutinin studies and viral cultures especially for neurotropic viruses—including herpes simplex and coxsackie —were negative.

The patient was diagnosed as having coccidioidomycosis and it was decided to use intravenously administered amphotericin B and to not do cisternal injection but to give amphotericin B intrathecally by lumbar puncture. Intravenous administration of amphotericin B was started at 0.5 mg per kg of body weight every day and intrathecal administration at 0.5 mg every other day. The treatment plan was to continue giving amphotericin B intrathecally by lumbar puncture for a total dose of 15 mg, while gradually increasing the intravenous dose to 1 mg per kg of body weight. Acetylsalicylic acid, 180 mg four times a day, and trimethobenzamide hydrochloride (Tigan®), 100 mg capsules three times a day, were given to combat fever, vomiting and headache associated with amphotericin B administration. No other medications were used to tranquilize the patent and only a 1 percent solution of xylocaine was injected intradermally at the lumbar puncture site. To evaluate any toxic effects of amphotericin B, the patient's hematocrit, electrolytes, magnesium, creatinine, liver enzymes and urine were

monitored. After two weeks of therapy, the patient's hematocrit had fallen to 24; a transfusion of 200 ml of whole blood was given and the hematocrit increased to 32 and remained stable. Potassium supplements were started after eight days of therapy to stabilize serum potassium. After four weeks of therapy, while the patient was receiving 1 mg of amphotericin B per kg of body weight per day given intravenously, serum potassium levels had fallen to 2 mEq, and it was decided to stop amphotericin B for one day while the patient was given 40 mEq of potassium chloride intravenously. Following this, serum potassium levels rose to 3 mEq and intravenously administered amphotericin B was restarted at a daily dose of 0.75 mg per kg of body weight. Intrathecally administered amphotericin B was maintained at 0.5 mg every other day. Additionally, oral potassium supplements were increased to 40 mEq daily. The patient's clinical status continued to improve during the stay in hospital. Following the decreased amphotericin B dosage schedule, the hematocrit and potassium levels remained stable. At no time was the intrathecal administration of amphotericin B by lumbar puncture a technical or clinical problem. The child cooperated in the procedure and did not have any signs of irritation following injection. Examination of the cerebrospinal fluid after two months of therapy showed 24 cells, two thirds of which were lymphocytes. CSF glucose was 35 and CSF protein 23 mg per 100 ml. The patient's pleasant disposition returned, there was no irritability or lethargy and ataxia disappeared. Head circumference remained within normal limits. Repeated biweekly coccidioidymcosis skin tests showed only 1 cm of erythema and no significant induration at 24 and 48 hours.

The patient was discharged after two months of therapy, having received 30 intrathecal injections of amphotericin B for a total intrathecal dose of 15 mg. The total intravenous amphotericin B dose was 500 mg. After discharge, the patient received weekly injections of 0.5 mg amphotericin B in the spinal fluid and 9.5 mg intravenously.

After three months this dosage was given every other week for an additional three months. The therapy then was given monthly. Eighteen months after therapy was begun, amphotericin B was stopped. Complement fixation titers in the spinal fluid had remained negative during the 15 months of therapy, and sixteen months after cessation of therapy they have remained negative. Response to a coccidioidomycosis skin test became positive during the fourth month of therapy and currently is positive with 15 mm induration.

Clinically, the child had done well. Growth and development have been normal. There is no evidence of residual sequelae of meningitis or any signs of drug toxicity. The creatinine level was 0.6 mg per 100 ml and serum complement fixation was 3 plus at 1:8 for coccidioidomycosis.

## Comment

Since the introduction of amphotericin B for parenteral administration in 1957, there have been numerous reports of its successful use in the treatment of patients with disseminated coccidioidomycosis.[1,2] The present case report shows that a child with coccidioidal meningitis can be successfully managed by a combination of intravenous and intrathecal (lumbar) administration of amphotericin B. Lumbar puncture administration was adequate to eradicate the disease and cisternal tap was not needed. Coccidioidal meningitis is one of the major causes of chronic granulomatous meningitis and, if untreated, is uniformly fatal. One must always consider this disease when there is an insidious onset of headache, nuchal rigidity and signs of confusion or drowsiness. Although this would apply especially to children residing in endemic areas such as California or the southwestern United States, with the widespread travels of families today, inquiries should be made about any temporary visit to endemic areas. Characteristically, examination of cerebrospinal fluid gives findings of a granulomatous meningitis with elevated protein, low CSF sugar and pleocytosis with mononuclear predominance. Most often the organism is not recovered from the cerebrospinal fluid and there usually are no other foci of coccidioidal infections observed. The diagnosis is confirmed by serological examination of the blood and spinal fluid for precipitating and complement fixing antibodies to coccidioides. A skin test usually gives negative results during dissemination of coccidioidmycosis and therefore is not a reliable sign of infection. A rising complement fixation antibody titer or a titer greater than 1:32 with a negative skin test, suggests dissemination of the disease or an imminent danger of dissemination and requires immediate therapy. Any complement fixation titers found in the cerebrospinal fluid are diagnostic of coccidioidal meningitis or extradural coccidioidal lesion because these antibodies do not usually cross into the CSF from the serum.[3]

During the course of therapy, a falling complement fixation antibody titer and a positive coccidioidal skin test indicate an excellent response to therapy and a favorable prognosis.

It is agreed that prolonged administration of amphotericin B is required to prevent recrudescence of the meningitis. In this case, therapy was given for 18 months. Amphotericin B in the serum does not pass the blood-brain barrier in adequate amounts, but it may mask meningitis during intravenous treatment. All children with signs of disseminated coccidioidomycosis should have a lumbar puncture done before receiving amphotericin B since early treatment directed against the central nervous system infection is mandatory. Coccidioidal meningitis must be treated by intrathecal administration of the drug. Doses of 0.5 mg every other day are often necessary. Concurrently, amphotericin B is given intravenously starting at a low dose (0.25 mg per kg of body weight) and increasing to 1 mg per kg of body weight if tolerated. The patient reported here tolerated only 0.75 mg per kg every other day.

Recently, Glynn and coworkers reported the use of intrathecal (lumbar) administration of amphotericin B with hyperbaric glucose and stressed the dangers of cisternal tap; before the present report, intrathecal administration of amphotericin B was felt to be effective only when given by cisternal puncture or the use of an intraventricular reservoir.[4-6]

It is noteworthy that the child reported in this case history was treated by repeated lumbar punctures without any special solutions and this offered no technical problems. The child was given only acetylsalicylic acid and trimethobenzamide hydrochloride medication. Arachnoiditis was not noted, and the response to therapy was excellent.

## Summary

A 2¾-year-old boy was coccidioides immitis meningitis was successfully treated by the combined use of amphotericin B given intrathecally by lumbar puncture and intravenously over an 18-month period. Cisternal tap was not needed to eradicate the infection. Clinical improvement was pronounced and no serious complication of therapy was encountered. Sixteen months after cessation of therapy, the patient remains in excellent health with no evidence of residual disease or damages.

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